

Original Article

# Randomized, prospective assessment of moisturizer efficacy for the treatment of radiation dermatitis following radiotherapy after breast-conserving surgery

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## Abstract

**Objective:** The effect of heparinoid moisturizer use after acute skin damage for patients receiving whole-breast radiotherapy after lumpectomy is understudied.

**Methods:** A total of 30 patients were randomly assigned to receive heparinoid moisturizer (Group M), and 32 patients comprised the control group (Group C). Patients in Group M were instructed to apply heparinoid moisturizer from 2 weeks following whole-breast radiotherapy, and to continue to use the moisturizer until 3 months after completion of whole-breast radiotherapy. Group C patients were instructed to not apply any topical moisturizer during the study period. The relative ratio of skin water content ratio ( $RWCR_{(t)} = (I_t/N_t)/(I_0/N_0)$ ) between irradiated and non-irradiated field was calculated. Signs and symptoms were also assessed. The primary endpoint was the difference in relative ratio of skin water content ratio between 2 and 4 weeks following whole-breast radiotherapy.

**Results:** In Group C, relative ratio of skin water content ratio dropped to  $0.80 \pm 0.15$  at 2 weeks and maintained the low level at 4 weeks following whole-breast radiotherapy. Similarly, in Group M, relative ratio of skin water content ratio dropped to  $0.81 \pm 0.19$  at 2 weeks (prior to application), however, it returned to baseline level ( $1.05 \pm 0.23$ ) at 4 weeks (2 weeks after application). The arithmetic difference of relative ratio of skin water content ratio in Group M was  $0.24 \pm 0.23$  and was significantly larger than in Group C ( $0.06 \pm 0.15$ ;  $P < 0.01$ ). Skin dryness and desquamation were less severe in Group M.

**Conclusions:** The application of heparinoid moisturizer for 2 weeks following whole-breast radiotherapy significantly increased water content and helped improve skin dryness and desquamation compared with no use of moisturizer.

**Key words:** breast cancer, radiation dermatitis, skin hydration, emollients, randomized controlled trial

## Introduction

Acute radiation dermatitis (ARD) is one of the most common side effects of radiotherapy (RT) for breast cancer. ARD is caused partly by damage to the skin and appendages, and associated symptoms include hair loss, dryness and itching (1). In normal healthy skin, the epidermis and its outermost stratum corneum layer act as a barrier to water loss, and thereby maintain skin hydration (2). The epidermis is primarily composed of stratifying layers of keratinocytes which are highly radiosensitive. Radiation skin injury involves immediate damage to basal keratinocytes and hair follicle stem cells, followed by DNA breaks and inflammation (3). Additionally, eccrine sweat glands are very radiosensitive compared with the epidermis (4) and skin water content (WC) is influenced by eccrine sweating in regions rich in sweat glands (5). As a result of barrier dysfunction, irradiated skin often feels drier compared with non-irradiated skin. However, it is evident that few systematic studies have been published on this topic.

To date, a number of studies performed have each failed to show a beneficial effect of skin care products to reduce or prevent ARD (6,7). Although guidelines on the use of skin care during the course of RT remain somewhat inconsistent, moisturizers are currently often used in clinical practice in western countries for patients undergoing RT for breast cancer (8). In Japan, however, topical agents for Grade 1 dermatitis are not traditionally prescribed by most radiation oncologists unless the patient complains of symptoms such as itching and pain. In 2012, the JASTRO (Japanese Society for Radiation Oncology) Research Group distributed a booklet about skin care during and after breast RT. Without sufficient evidence, it recommended moisturizer use for dryness after RT. An investigation into the effectiveness of moisturizers in the early phase of ARD, when dryness is one of the main symptoms, therefore represents an important and timely clinical issue.

The heparinoid moisturizer, Hiruoid® (Maruho, Osaka, Japan) contains mucopolysaccharide polysulphate (at 0.3% w/w), which is structurally closely related to components of the connective tissue. It has been widely used in Japan to treat dry skin, and especially for the treatment of atopic dermatitis (9).

The present study evaluated the effect of this heparinoid moisturizer on skin WC after whole-breast radiotherapy (WBRT) using the corneometer, a simple instrument and a valid tool for assessing skin moisture (10). It measures the electrical capacitance of the skin surface as an indicator of stratum corneum hydration, which is dependent on the high dielectrical constant of WC relative to other skin components. The corneometer has been demonstrated to be useful for objectively assessing radiation induced skin reactions for breast cancer patients (11). Skin-related signs and symptoms were also assessed.

## Patients and methods

### Patients

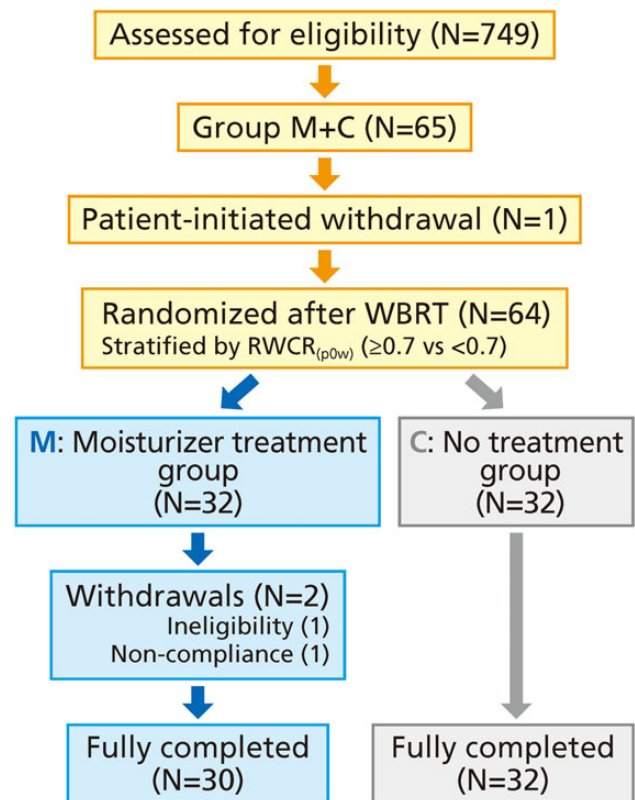
Women aged 30–65 years with non-inflammatory breast cancer or carcinomas *in situ* treated by lumpectomy were included. The tumor location was outside the inner-upper quadrant, which was designated as a skin WC measurement site. Exclusion criteria included patients who had: bilateral breast cancer; previous RT to the thorax; wide-spreading skin disease; collagen vascular disease; sensitivity to heparinoid substance; and patients who did not keep to the instructions on how to apply the topical agents on the breast. A compliance rate of 60% was set to the lower limit for acceptance.

## Moisturizer treatment

All patients underwent individualized computed tomography-based treatment planning using the field-in-field technique (12) and efforts were made to ensure that the breast treatment volume received was not <95% or >107% of the prescribed dose. Standard fractionation (2 Gy per session, five sessions per week) was used. The entire ipsilateral breast was irradiated with two opposing tangential fields with a total dose of 48–50 Gy with photons (4–6 MV). According to the pathologic report, the primary tumor bed was boosted with a total dose of 10–18 Gy with electrons (4–16 MeV). After a pre-treatment evaluation, patients were instructed to not apply any moisturizer until 2 weeks following WBRT, and randomly assigned to either no further moisturizer (C) or treatment with the heparinoid moisturizer (M). Randomization was stratified according to the relative ratio of skin WC ratio ( $RWCR_{(p0w)}$ ) on the last day of WBRT ( $\geq 0.7$  vs  $< 0.7$ ). Patients in Group M were instructed to apply the heparinoid moisturizer twice daily from 2 weeks following WBRT, and to continue to use the heparinoid moisturizer twice daily for 3 months after completion of WBRT. The treatment period totaled approximately 10 weeks. Group C patients were instructed to not apply any topical moisturizer during the study period (Fig. 1). However, all patients with itchy or reddened skin were allowed to use topical corticosteroids.

## Ethical considerations

The study was approved by the institutional review board (11-R060). Consent was obtained from all patients, and signed copies of the consent form were provided to each of these patients.



**Figure 1.** Consort trial flow diagram. WBRT, whole-breast radiotherapy;  $RWCR_{(p0w)}$ , relative ratio of skin WC ratio on the last day of WBRT.

## Study outcomes

### Measurement of skin WC

On the day of measurement, patients were instructed not to bathe in the morning and to not apply any products to the bilateral breast. Sebum from the breast skin surface was measured via sebumeter<sup>®</sup> following a minimum of 20 min bed rest. After the skin was washed with hypoallergenic soap and wiped gently with lint-free cloth and dried well for 20 min, WC was measured using a corneometer CM825<sup>®</sup> (Courage + Khazaka, Cologne, Germany). The two designated areas for WC measurement were  $3 \times 3 \text{ cm}^2$  for each skin area analysis in an upper-inner quadrant of the irradiated breast, at least 2 cm apart from the midline. These areas had to be at least 2 cm away from the surgical wound and 1 cm away from the edge of boost (Fig. 2). WC was measured a total of five times at different points in each area, and the mean value of 10 measurements was used for analysis. For controls, the corresponding area of skin of the non-irradiated breast was measured in the same manner.

WC was measured prior to WBRT (baseline,  $t = 0$ ), on the last day of WBRT, and 2 weeks, 4 weeks and 3 months following WBRT. The pre-WBRT WC ratio ( $\text{WCR}_{(0)} = I_0/N_0$ , irradiated breast skin WC divided by contralateral breast WC) was calculated. Taking intra- and inter-individual variation (5) into account,  $\text{RWCR}_{(t)}$ , (WCR normalized by pre-WBRT state) was then calculated using the following formula (11)

$$\text{RWCR}_{(t)} = \frac{\text{WCR}_{(t)}}{\text{WCR}_{(0)}} = \frac{I_t/N_t}{I_0/N_0},$$

where  $I_0$  and  $I_t$  correspond to WC on the irradiated breast at pre-WBRT and each study point, and  $N_0$  and  $N_t$  correspond to WC on the non-irradiated breast at pre-WBRT and each study point.

We propose the following formula for moisture recovery (MR) 2 and 4 weeks following WBRT, which is the difference of  $\text{RWCR}_{(t)}$  over time.

$$\text{MR}_{p2w-p4w} = \frac{I_{p4w}/N_{p4w}}{I_0/N_0} - \frac{I_{p2w}/N_{p2w}}{I_0/N_0},$$

where  $I_{p2w}$ ,  $I_{p4w}$  corresponds to WC on the irradiated breast at 2 and 4 weeks following WBRT, and  $N_{p2w}$  and  $N_{p4w}$  correspond to WC on the non-irradiated breast. This arithmetic difference of these ratios of ratios can equate to a simple approximation of WC recovery from ARD in this interval.

### Clinical assessment

Signs associated with ARD (i.e. erythema, dryness and desquamation) were independently assessed by two personnel (i.e. radiation oncologist and dermatologist) using different scoring scales. The dermatologist used atopic dermatitis severity classification of

dryness and desquamation (13), while radiation oncologists assessed ARD using a simpler grading system. Both personnel used the same scale in the classification of erythema (Table 1). Radiation oncologists directly assessed ARD under direct vision, whereas the dermatologist, who was blinded for the treatment group assessed ARD via photographs.

Patients were asked to complete a patient diary, including questions about daily compliance of the topical agent and symptoms in the morning at the study point. It required patients to self-assess the degree of itching and pain within the irradiated field using a visual analog scale (VAS) ranging from 0 to 10 (length measured in cm). The VAS was changed to a scale ranging from 0 (none) to 100 (severe).

The primary endpoint was the difference in  $\text{RWCR}_{(t)}$  between 2 and 4 weeks following WBRT, which describes the efficacy of heparinoid moisturizer following WBRT. The secondary endpoint was to evaluate the efficacy of the heparinoid moisturizer on signs and symptoms of ARD.

### Statistical methods

According to Yamazaki et al. (11),  $\text{RWCR}_{(t)}$  immediately decreased after completion of RT to approximately 70% (SD 26) compared with pre-RT, and then recovered slowly to 0.8 four weeks following RT. It would be expected to recover to over 0.9 following moisturizer application. Assuming a SD of 0.15 for each at 4 weeks following RT, it was estimated that a sample of 36 patients was required in each group (M and C) with a two-sided  $\alpha$  of 0.05 and a statistical power of 80%. Accrual of 40 patients in each group was planned, since 10% of the patients were expected to be excluded from analysis.

Two sets of skin WC measurements between study points or groups, skin toxicity scores, VAS, and demographic factors were compared for differences using the Wilcoxon rank-sum test with Bonferroni's correction, Mann-Whitney  $U$  test, Student's  $t$ -test, and  $\chi^2$  test, and all  $P$ -values expressed are two-sided with statistical significance evaluated at the 0.05  $\alpha$  level. Statistical analyses were performed using SPSS software (IBM SPSS statistics 21; IBM Corp, New York, NY, USA). The completed study is registered with UMIN-CTR5532.

## Results

From April 2011 to April 2013, a total of 749 patients diagnosed with early breast cancer were prescribed RT at the St. Luke's International Hospital. Accrual was stopped 9 months after the initial scheduled accrual period of 2 years and 4 months, without reaching the previously expected number. Sixty-five patients consented to participate in this trial. There were three withdrawals: consent decline ( $n = 1$ ); ineligibility due to heparinoid moisturizer use before second randomization ( $n = 1$ ); and noncompliance with study procedures ( $n = 1$ ). Thirty patients remained on the interventional moisturizer Group (M), and 32 patients on the control group (C) (Fig. 1).

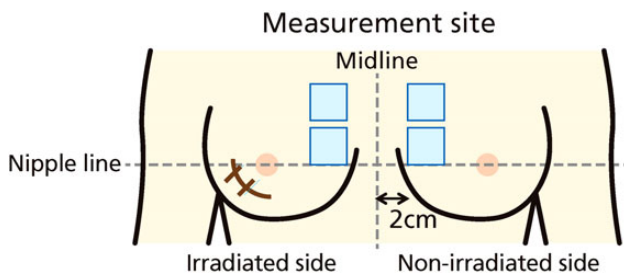


Figure 2. Measurement site for water content.

Table 1. Severity scoring system for acute radiation dermatitis

Severity	Dryness and desquamation		Erythema
	Dermatologist (D)	Radiation oncologist (RO)	D and RO
0	None	None	None
1	Mild	Mild	Faint
2	Moderate	Moderate-severe	Moderate
3	Severe	—	Brisk
4	Very severe	—	—

**Table 2.** Patient and treatment characteristics

	Group M N = 30	Group C N = 32	P*
Age (mean ± SD)	48.3 ± 8.1	51.6 ± 7.2	0.09
Affected breast			
Right	12	18	
Left	18	14	0.20
Tumour location			
Lateral	28	28	
Inner	0	3	
Central	2	1	0.20
Breast size: CTV (cm <sup>3</sup> ) (mean ± SD)	401.3 ± 53.5	330 ± 137.1	0.08
V <sub>107%</sub> (%) (mean ± SD)	1.75 ± 24.0	0.41 ± 0	0.23
Chemotherapy before RT	4	4	0.92
Endocrine therapy	3	1	0.27
Boost			
10–18 Gy	15	16	
No boost	15	16	0.99
Energy			
4 MV	18	24	
6 MV	12	8	0.21
Regional node irradiation: treated	2	0	0.23
Smoker			
Never	24	26	
Former	6	5	
Current	0	1	0.58
Body mass index (mean ± SD)	22.5 ± 3.6	21.2 ± 3.2	0.14
Topical corticosteroids use in the treated breast during or after RT	8	9	0.90

CTV (cm<sup>3</sup>), clinical target volume (=breast tissue); V<sub>107%</sub> (%), breast volume receiving 107% of prescribed dose; RT, radiotherapy.

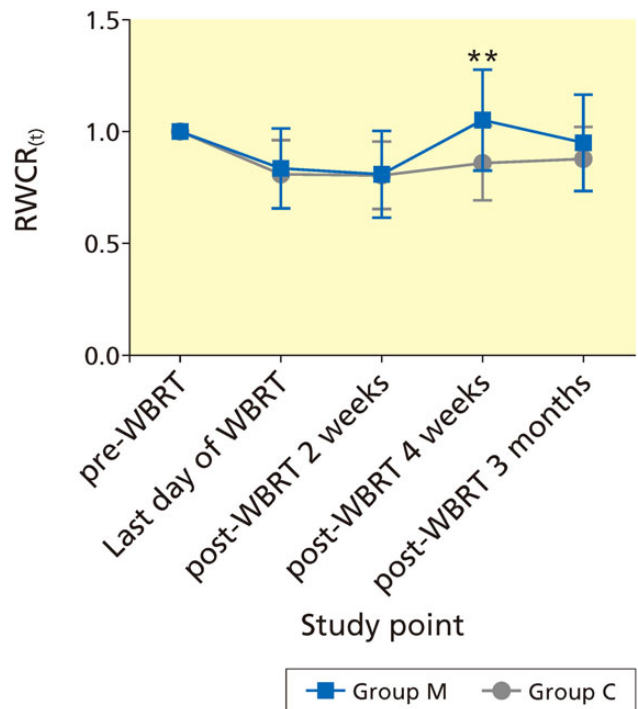
\*Student's *t*-test,  $\chi^2$  test.

Patient and treatment characteristics are listed in Table 2. In spite of the small number of patients, the characteristics were similar with respect to age, tumor location, breast volume, adjuvant therapy, boost dose, photon energy, smoking history and body mass index. Each group was almost identical with the number of topical steroid use in the treated breast.

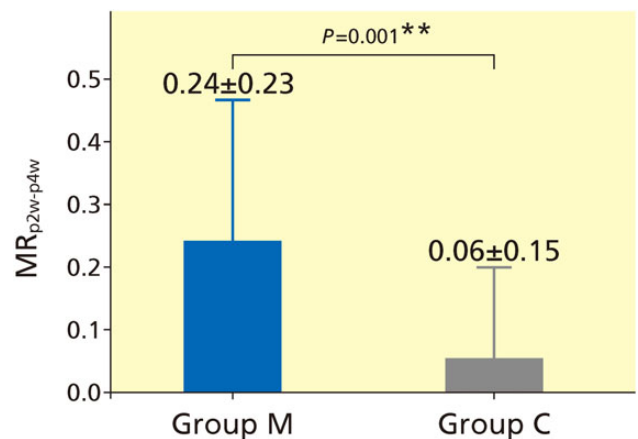
### Time-course of RWCR<sub>(t)</sub>

WC values in the non-irradiated breast generally continued to be constant between 37 and 44 arb. unit through the study period. In both groups, RWCR<sub>(t)</sub> decreased to the same level at the last day of WBRT and 2 weeks following WBRT, according to the stratification. Overall, RWCR<sub>(t)</sub> at 0 and 2 weeks following WBRT were significantly lower than baseline ( $0.82 \pm 0.16$ ,  $P < 0.01$  and  $0.81 \pm 0.17$ ,  $P < 0.01$ , respectively). In Group C, RWCR<sub>(t)</sub> remained at  $0.86 \pm 0.17$  at 4 weeks following WBRT and maintained a significantly lower level until 3 months ( $0.88 \pm 0.14$ ,  $P < 0.01$ ). In contrast, RWCR<sub>(t)</sub> in Group M returned to a baseline level ( $1.05 \pm 0.23$ ,  $P = 1.00$ ) at 4 weeks following WBRT (after 2 weeks application). At 3 months following WBRT, approximately 10 weeks of moisturizer treatment, RWCR<sub>(t)</sub> was slightly decreased ( $0.95 \pm 0.22$ ,  $P = 0.69$ ). A statistically significant difference ( $P = 0.01$ ) was noted between two groups at 4 weeks following WBRT (2 weeks application in Group M); this significant difference was not apparent, however, at 3 months ( $P = 0.11$ ) (Fig. 3, Supplementary Material S1).

MR between 2 weeks and 4 weeks, the primary endpoint was  $0.24 \pm 0.23$  in the moisture group, which was significantly larger than in the control group ( $0.06 \pm 0.15$ ,  $P = 0.001$ ) (Fig. 4).



**Figure 3.** Time-course of relative water content ratio (RWCR<sub>(t)</sub>). \*\*Statistically significant by Mann–Whitney *U* test.

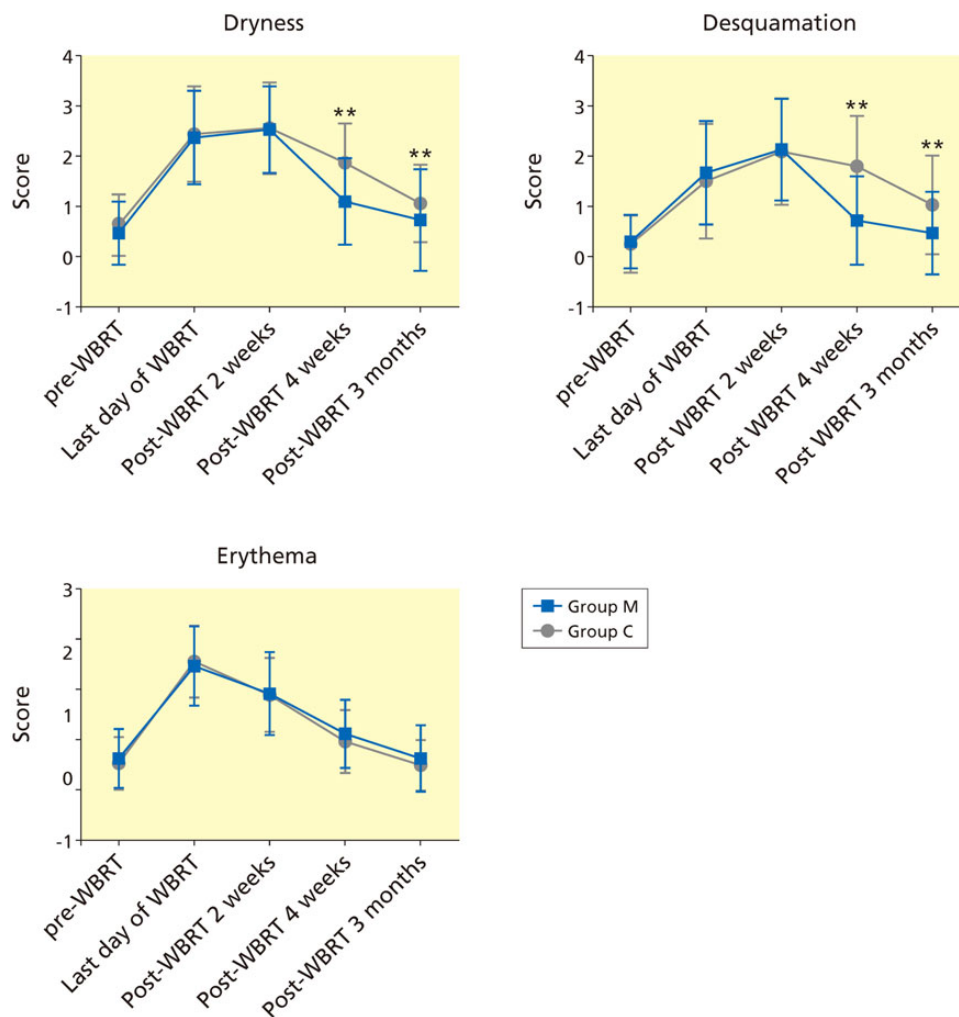


**Figure 4.** Moisture recovery between 2 and 4 weeks (MR<sub>p2w-p4w</sub>) following WBRT. \*\*Statistically significant by Mann–Whitney *U* test.

### Clinical assessment

The skin toxicity score graded by the dermatologist was evaluated (Supplementary Material S2). At the end and at 2 weeks following WBRT, all symptom scores were significantly higher compared with the scores at pre-WBRT period. Maximal dryness and desquamation were observed at 2 weeks following WBRT. On the other hand, erythema was at its most severe at the last day of WBRT. No different time-course pattern was noted in three kinds of skin toxicity. However, at 4 weeks and 3 months following WBRT, dryness and desquamation in the irradiated field were significantly less in Group M, compared with Group C. In contrast, there was no significant difference between two groups in erythema through the study period (Fig. 5).

The skin toxicity score by radiation oncologists was almost identical to the score made by the dermatologist (data not shown).



**Figure 5.** Grading score of ARD signs in Group M and Group C assessed by a dermatologist; ARD, acute radiation dermatitis \*\*Statistically significant by Mann-Whitney *U* test.

Skin symptom scores were generally low (Supplementary Material S3). The itching VAS score was highest at the last day of or 2 weeks following WBRT, but improved at 4 weeks and 3 months following WBRT in both groups. The itching scores in Group C were significantly higher than the pre-WBRT period until 3 months following WBRT, however, they showed no significant difference compared with the pre-WBRT period after 4 weeks in Group M.

The time-course of pain score denoted the same tendency as itching, and pain scores in Group C were significantly higher than the pre-WBRT period until 4 weeks following WBRT. In contrast, pain scores in Group M showed no difference after 4 weeks. Comparisons between two groups revealed that pain scores in Group M were significantly lower compared with those in Group C at 3 months following WBRT ( $P = 0.03$ ) (Fig. 6).

One patient experienced temporary eczema that seemed to be unrelated to the use of the heparinoid and was able to continue to apply the heparinoid without further symptoms.

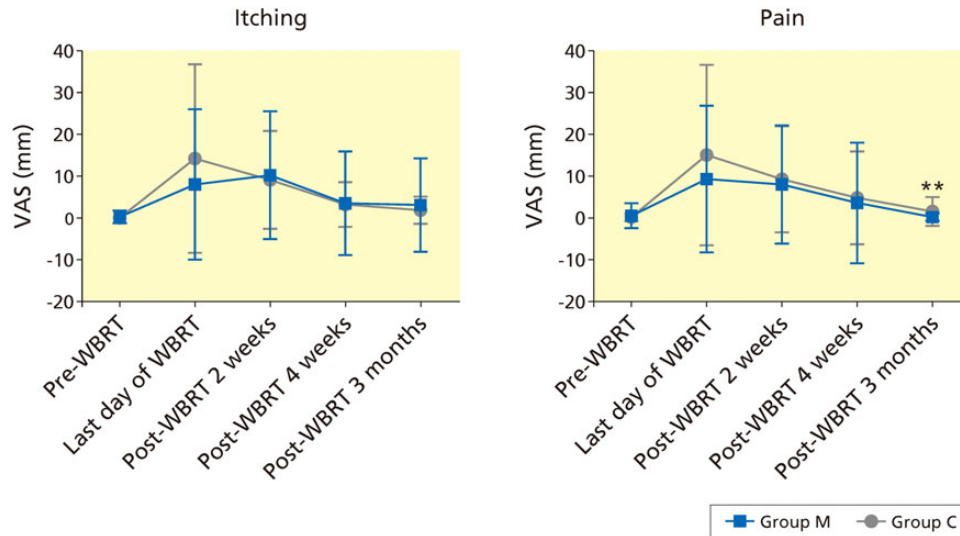
## Discussion

Radiotherapy is a critical component in the breast conserving therapy of breast cancer but is often associated with bothersome ARD that can cause significant discomfort.

Currently, no medication exists that effectively mitigates or prevents ARD (3,14). Evidence from a limited number of randomized controlled trials (RCTs) does not support the use of topical *Aloe vera* (15), trolamine (16), calendula cream (17), sucralfate cream (18), hyaluronic acid (19) or silver sulfadiazine (20). In a pooled analysis, the use of topical corticosteroid was associated with a significantly lower incidence of Grade 3 dermatitis ( $P = 0.01$ ) (21). However, the incidence of Grade 3 dermatitis is low in association with breast conserving therapy. The use of steroidal agents is limited because it can cause thinning (22) of the skin and introduce bacterial infections (23).

Regarding the time-course of stratum corneum WC in irradiated field, several reports using the corneometer exist. Recently, Hu et al. (2) demonstrated a significant decrease of stratum corneum hydration in 144 breast cancer patients undergoing RT. In this prospective study, the skin hydration dropped from 86 to 64 arb. unit on the last day of RT. Yamazaki et al. (11) also analyzed  $RWCR_{(t)}$  in 35 patients and found an immediate decrease to 0.71 at the last day of RT, recovering to 0.82, 0.87 and 0.92 at 1, 3 and 12 months post-WBRT, respectively. In the present study,  $RWCR_{(t)}$  significantly decreased to  $0.82 \pm 0.16$  at the last day of WBRT and this low level continued until 3 months following WBRT in Group C ( $0.88 \pm 0.14$ ). In an earlier study, Jensen et al. (24) reported a similar time-course





**Figure 6.** Grading score of ARD symptoms in Group M and Group C assessed by VAS. RT, radiotherapy. \*\*Statistically significant by Mann–Whitney *U* test.

of skin WC following RT in irradiated field and cream-untreated field.

In the present study, the efficacy of the heparinoid moisturizer which is widely used for skin dryness of atopic dermatitis in Japan (9) was evaluated following RT. Jensen et al. (24) also evaluated the efficacy of an oil-in-water emulsion in a randomized study with 66 breast cancer patients. Reduced hydration values in the irradiated fields improved more quickly in the cream-treated group compared with untreated controls. The application of heparinoid moisturizer for 2 weeks significantly increased  $RWCR_{(t)}$ , and MR between 2 and 4 weeks to a significantly greater extent than in the control group. However, there was no significant difference of  $RWCR_{(t)}$  at 3 months after WBRT (Group M:  $0.95 \pm 0.22$  vs Group C:  $0.88 \pm 0.14$ ,  $P = 0.11$ ). A marginally lower compliance rate in applying the heparinoid moisturizer at 3 months compared with that at 4 weeks following WBRT ( $P = 0.053$ ) may have contributed to this reduction in difference between groups at 3 months. The slow recovery of  $RWCR_{(t)}$  following WBRT in the irradiated field was noted, consistent with the time-course reported by other investigators (11,24). This may also have contributed to the small difference between groups at 3 months. In fact, WC appeared to return to pre-RT state after 6 months following WBRT in spite of the small number of patients (data not shown).

It is well-known that breast cancer patients following WBRT suffer from skin dryness and itching (1). The severity of signs of ARD, such as dryness and desquamation, which was evaluated by the experienced dermatologist, correlated well with  $RWCR_{(t)}$  values. Those signs were milder in the treatment group. At 4 weeks (i.e. after 2 weeks application) and 3 months following WBRT, dryness and desquamation in the irradiated field were significantly less in Group M compared with controls. One of the reasons why the difference became smaller at 3 months may be due to putative spontaneous recovery of the stratum corneum WC.

There was no difference between the time-course of erythema score. Jensen et al. also noted no effect of oil-in-water emulsion on the skin score involving erythema and desquamation at 1 week following RT. However, the skin score marginally improved by the emulsion at  $47 \pm 7$  days following treatment (24). Moisturizer is therefore considered to have subtle or little effect on inflammatory changes.

Although the use of the heparinoid moisturizer also helped alleviate the pain related to ARD, symptoms were already generally mild and the actual influence of heparinoid moisturizer on pain reduction remains to be determined. In our study, the moisturizer did not alleviate itching. In contrast, Jensen et al. (24) reported a significant decrease in itching score at an early phase following the immediate application of oil-in-water emulsion after RT. Collectively, these findings suggest that the early application of moisturizer may be warranted. However, in this study, the heparinoid moisturizer was started from 2 weeks following WBRT as it was thought to be more appropriate at that point for measurement of WC using the corneometer compared with at the end of WBRT, when inflammatory change was more likely to have subsided.

Di Franco et al. measured skin WC using the corneometer and evaluated skin-related symptoms regularly before, during and 1 month after RT for 100 breast cancer patients who had applied moisturizing cream twice a day starting 15 days before and 1 month after RT. The use of moisturizers increased skin WC after the application period, and reduced the incidence of RT-associated skin side effects. All five different moisturizing creams used in the study were reported to be equally valid (8). In contrast to their study, our exploratory study demonstrated the prophylactic application of a moisturizer adequately supplemented skin WC and sebum after WBRT. However, WC significantly decreased at the last day of WBRT in spite of starting treatment with the heparinoid moisturizer at the beginning of RT (25). Unfortunately, the reasons for this difference could not be analyzed as details about WC measurement are unknown in the study of Di Franco et al. (8). The sebum decreased until at least 1 year after WBRT; however, it was observed to be sustained throughout the study period associated with the prophylactic use of heparinoid moisturizer (25). The long-term application of moisturizer before and after RT may alleviate barrier dysfunction by supplementing WC in the early phase and the sebum.

The present study had a number of limitations. The major challenge was the level of compliance, and although compliance was high at the baseline, it decreased over subsequent assessments by the diary method. In most cases, it remained within acceptable limits, with just one patient excluded. Furthermore, although the effect of RT on the non-irradiated skin was expected to be negligibly small, the

distance of  $\geq 2$  cm from the field edge was insufficient. According to Epstein et al. (26), the surface dose of contralateral breast 2–4 cm from the midline receives 3–12% of the prescribed dose. In fact, the sebum level measured by the sebumeter in the opposite breast skin (at least 2 cm away from the midline) was significantly decreased (data not shown). Fortunately, the WC value was minimally affected by low dose RT. A third limitation concerned the potential impact of the heparinoid moisturizer on skin WC measurement. In this regard, it should be noted that patients were carefully instructed with regard to the study procedures, washed the skin with soap, and wiped and dried the skin adequately enough prior to any measurements in order to minimize this potential effect.

The present study also has several notable strengths, including the use of an established instrument in the analysis of skin WC. To our knowledge, this is the first study to report the effectiveness of moisturizer confirmed by RCT. Our study therefore provides some evidence on the efficacy of heparinoid moisturizer following WBRT.

Furthermore, skin appearance was independently evaluated in RCT by radiation oncologists and an expert dermatologist blinded for the treatment group. Actually, the findings by a dermatologist were almost identical to those of radiation oncologists under direct vision.

In conclusion, the present study has shown that skin WC significantly decreased to at least 3 months after the completion of WBRT. Treatment with heparinoid moisturizer for 2 weeks following WBRT significantly increased skin WC, and helped to improve skin dryness and desquamation. These observations support the use of heparinoid moisturizer for breast cancer patients undergoing WBRT, although confirmatory evidence is required in order to further understand the potential clinical benefits of this low risk intervention. The findings regarding prophylactic use warrant a next phase of study investigating the protective effect for ARD using heparinoid moisturizer in a randomized setting.

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## Conflict of interest statement

None declared.

## References

- McQuestion M. Evidence-based skin care management in radiation therapy: clinical update. *Semin Oncol Nurs* 2011;27:e1–17.
- Hu SC, Hou MF, Luo KH, et al. Changes in biophysical properties of the skin following radiotherapy for breast cancer. *J Dermatol* 2014; 41:1087–94.
- Ryan JL. Ionizing radiation: the good, the bad, and the ugly. *J Invest Dermatol* 2012;132(3 Pt 2):985–93.
- Johns H, Morris WJ, Joiner MC. Radiation response of murine eccrine sweat glands. *Radiother Oncol* 1995;36:56–64.
- Pinnagoda J, Tupker RA, Agner T, Serup J. Guidelines for transepidermal water loss (TEWL) measurement. A report from the Standardization Group of the European Society of Contact Dermatitis. *Contact Dermatitis* 1990;22:164–78.
- Zhang Y, Zhang S, Shao X. Topical agent therapy for prevention and treatment of radiodermatitis: a meta-analysis. *Support Care Cancer* 2013;21: 1025–31.
- Sharp L, Johansson H, Landin Y, Moegelin IM, Bergenmar M. Frequency and severity of skin reactions in patients with breast cancer undergoing adjuvant radiotherapy, the usefulness of two assessment instruments—a pilot study. *Eur J Cancer* 2011;47:2665–72.
- Di Franco R, Sammarco E, Calvanese MG, et al. Preventing the acute skin side effects in patients treated with radiotherapy for breast cancer: the use of corneometry in order to evaluate the protective effect of moisturizing creams. *Radiat Oncol* 2013;8:57.
- Kawakami T, Soma Y. Questionnaire survey of the efficacy of emollients for adult patients with atopic dermatitis. *J Dermatol* 2011;38:531–5.
- Blichmann CW, Serup J. Assessment of skin moisture. Measurement of electrical conductance, capacitance and transepidermal water loss. *Acta Derm Venereol* 1988;68:284–90.
- Yamazaki H, Yoshida K, Kotsuma T, et al. Longitudinal practical measurement of skin color and moisture during and after breast-conserving therapy: influence of neoadjuvant systemic therapy. *Jpn J Radiol* 2009;27:309–15.
- de la Torre N, Figueroa CT, Martinez K, Riley S, Chapman J. A comparative study of surface dose and dose distribution for intact breast following irradiation with field-in-field technique vs. the use of conventional wedges. *Med Dosim* 2004;29:109–14.
- Yoshida H, Aoki T, Furue M, et al. English version of the interim report published in 1998 by the members of the Advisory Committee on Atopic Dermatitis Severity Classification Criteria of the Japanese Dermatological Association. *J Dermatol* 2011;38:625–31.
- Wong RK, Bensadoun RJ, Boers-Doets CB, et al. Clinical practice guidelines for the prevention and treatment of acute and late radiation reactions from the MASCC Skin Toxicity Study Group. *Support Care Cancer* 2013;21:2933–48.
- Richardson J, Smith JE, McIntyre M, Thomas R, Pilkington K. *Aloe vera* for preventing radiation-induced skin reactions: a systematic literature review. *Clin Oncol (R Coll Radiol)* 2005;17:478–84.
- Elliott EA, Wright JR, Swann RS, et al. Phase III Trial of an emulsion containing trolamine for the prevention of radiation dermatitis in patients with advanced squamous cell carcinoma of the head and neck: results of Radiation Therapy Oncology Group Trial 99–13. *J Clin Oncol* 2006;24: 2092–7.
- Sharp L, Finnila K, Johansson H, Abrahamsson M, Hatschek T, Bergenmar M. No differences between Calendula cream and aqueous cream in the prevention of acute radiation skin reactions—results from a randomised blinded trial. *Eur J Oncol Nurs* 2013;17:429–35.
- Wells M, Macmillan M, Raab G, et al. Does aqueous or sucralfate cream affect the severity of erythematous radiation skin reactions? A randomised controlled trial. *Radiother Oncol* 2004;73:153–62.
- Kirova YM, Fromantin I, De Rycke Y, et al. Can we decrease the skin reaction in breast cancer patients using hyaluronic acid during radiation therapy? Results of phase III randomised trial. *Radiother Oncol* 2011;100: 205–9.
- Hemati S, Asnaashari O, Sarvizadeh M, et al. Topical silver sulfadiazine for the prevention of acute dermatitis during irradiation for breast cancer. *Support Care Cancer* 2012;20:1613–8.
- Meghrajani CF, Co HC, Ang-Tiu CM, Roa FC. Topical corticosteroid therapy for the prevention of acute radiation dermatitis: a systematic review of randomized controlled trials. *Expert Rev Clin Pharmacol* 2013; 6:641–9.
- Kolbe L, Kligman AM, Schreiner V, Stoudemayer T. Corticosteroid-induced atrophy and barrier impairment measured by non-invasive methods in human skin. *Skin Res Technol* 2001;7:73–7.
- Chan RJ, Larsen E, Chan P. Re-examining the evidence in radiation dermatitis management literature: an overview and a critical appraisal of systematic reviews. *Int J Radiat Oncol Biol Phys* 2012;84:e357–62.

- 
24. Jensen JM, Gau T, Schultze J, et al. Treatment of acute radiodermatitis with an oil-in-water emulsion following radiation therapy for breast cancer: a controlled, randomized trial. *Strahlenther Onkol* 2011;187:378–84.
  25. Ogita M, Sekiguchi K, Akahane K, et al. Randomized, prospective trial of moisturizer efficacy for the treatment of skin dryness following radiotherapy after breast-conserving surgery. *Int J Radiat Oncol Biol Phys* 2014;90:S248–9.
  26. Epstein RJ, Kelly SA, Cook M, et al. Active minimisation of radiation scatter during breast radiotherapy: management implications for young patients with good-prognosis primary neoplasms. *Radiother Oncol* 1996;40:69–74.